REMARKS

Claims 37-56 and 74-78 are pending and stand rejected, and claims 57-73 stand withdrawn. Claim 37 is amended herein to recite a conjugate of hydroxyalkylstarch (HAS) and a low molecular weight substance, obtained by a process that comprises selectively coupling (i) the terminal aldehyde group of a HAS molecule, or a functional group derived from this aldehyde group by chemical reaction, with (ii) a functional group on the low molecular weight substance, which is able to react with the aldehyde group of the HAS molecule or the functional group derived therefrom, wherein the coupling reaction results in a covalent bond between the terminal aldehyde of the HAS molecule or the functional group derived therefrom and the low molecular weight substance functional group, or wherein the coupling reaction is modified by a further reaction to give the abovementioned covalent bond. In addition, claims 37, 40-47, 74, 75, 77, and 78 are amended to replace the term "hydroxyalkylstarch" with "HAS," and a typographical error has been corrected in claim 38.

Support for the amendment to claim 37 can be found throughout Applicants' specification. *See*, for example, the specification at page 4, line 32 to page 5, line 2; page 8, lines 23-24; page 9, lines 17-27; page 9, line 35 to page 10, line 2; page 10, lines 10-12 and 23-27; and page 11, lines 28-31. Each of these sections discloses that the HAS functional group involved in the coupling reaction is *the* terminal aldehyde group or a functionality derived therefrom, and that the terminal aldehyde is *selectively* oxidized and then reacted with the low molecular weight substance. Thus, it is clear that the terminal aldehyde is selectively used in the presently recited coupling reactions, and no new matter is added by these amendments.

In light of these amendments and the following remarks, Applicants respectfully request reconsideration and allowance of claims 37-56 and 74-78.

Rejections under 35 U.S.C. § 102

The Examiner maintained the rejection of claims 37-45, 47, 48, 50, 52, 56 and 74-78 under 35 U.S.C. § 102(b), alleging that they are anticipated by Canadian Patent No. 2,233,725 (the Adamson publication). In particular, the Examiner asserted that there is no indication in the Adamson publication that aldehyde groups are not formed on the terminal unit of the HAS

disclosed therein. The Examiner also asserted that Applicants' specification does not clearly define the phrase "terminal aldehyde group of the hydroxyalkylstarch molecule."

Applicants respectfully disagree. The Adamson publication did not anticipate the previous claims. To further prosecution, however, independent claim 37 is amended herein to recite a conjugate of HAS and a low molecular weight substance, obtained by a process that comprises selectively coupling (i) the terminal aldehyde group of a HAS molecule, or a functional group derived from this aldehyde group by chemical reaction, with (ii) a functional group on the low molecular weight substance. Applicants submit that a person of ordinary skill in the art would understand that the phrase "terminal aldehyde group of HAS" refers to an aldehyde at the terminal saccharide unit of the HAS molecule, and no definition is necessary.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP § 2131. The Adamson publication does not disclose each and every element recited in the present claims. For example, the conjugates recited in present claim 37 result from a selective coupling between the terminal aldehyde group of HAS and a functional group of a low molecular weight substance. In contrast, the Adamson publication discloses HAS-hemoglobin conjugates obtained by conjugating hemoglobin to HAS that has been non-selectively modified with aldehyde groups, such that modification and coupling are *not limited to the terminal aldehyde. See*, e.g., page 3, line 31 to page 4, line 5, and page 8, lines 12-14, which disclose that to prepare HES for use in the method of Adamson, it is oxidized "so as to create thereon substantial numbers of aldehyde groups." At no point does the Adamson publication disclose a method or a conjugate in which hemoglobin is selectively coupled to the terminal aldehyde group of HAS.

With respect to independent claim 74 and the Examiner's assertion that the Adamson publication contains no indication that aldehyde groups are not formed on the terminal unit of the HAS disclosed therein, Applicants note that "[t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957." MPEP § 2112(IV) (emphasis in original). This section further states:

> To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted).

At no point does the Adamson publication indicate that a terminal aldehyde was necessarily formed, or that a conjugate was necessarily formed through such an aldehyde. Thus, terminal aldehyde groups were not inherently present in the HAS utilized by Adamson.

Further, all of the present claims require the HAS to be conjugated to a low molecular weight substance. The Examiner asserted that Applicants' previous arguments (filed on December 15, 2008) regarding the low molecular weight of the substance were not persuasive, because the claims do not recite the molecular weight of the substance. Applicants submit, however, that the recitation of a "low molecular weight" substance in the claims is in fact a sufficient recitation of the molecular weight. Further, as disclosed in Applicants' specification at page 13, lines 10-12, the phrase "low molecular weight substance" includes peptides of up to about 50 amino acids. Given an average molecular weight of 135 Daltons per amino acid residue, a peptide containing 50 amino acids would have a molecular weight of about 6750 Daltons, or 6.75 kDa, as one of ordinary skill in the art could immediately envisage. In contrast, the hemoglobin that is conjugated to HES as described by Adamson has a molecular weight of 64 kDa (*see*, page 1, lines 25-30), a molecular weight that is about *10-fold greater* than that described in Applicants' specification as "low molecular weight." As one of ordinary skill in the art would recognize, hemoglobin thus is clearly not a "low molecular weight substance" as described in the instant specification and recited in the present claims.

For at least the above reasons, the Adamson publication does not teach each and every element as recited in the present claims. As such, the present claims are novel over the Adamson publication.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 37-45, 47, 48, 50, 52, 56 and 74-78 under 35 U.S.C. § 102(b).

The Examiner maintained the rejection of claims 37-45, 47-56 and 74-78 under 35 U.S.C. § 102(b), alleging that they are anticipated by EP Patent No. 0 331 471 (the Larsen et al. patent) for reasons of record. The Examiner asserted that the remarks in Applicants' response filed on December 15, 2008, were not persuasive, because the "A" in the Larsen et al. formula can be a CO group, which would meet the requirement of the instantly claimed conjugate.

Applicants respectfully disagree. The Larsen et al. patent does not anticipate the present claims. Again, claim 37 recites conjugates formed by selectively coupling (i) the terminal aldehyde group of a HAS molecule, or a functional group derived from this aldehyde group by chemical reaction, with (ii) a functional group of a low molecular weight substance. Claim 74 recites that the binding interaction between the HAS molecule and the low molecular weight substance comprises at least one covalent bond between: (i) the terminal aldehyde group of the HAS molecule, or a functional group derived from the terminal aldehyde group, and (ii) a functional group of the low molecular weight substance. Contrary to the present claims, the polysaccharide (e.g., HAS) in the prodrugs of Larsen et al. is disclosed to be conjugated to the anti-inflammatory drug via any free hydroxyl group present in the polysaccharide molecule. *See*, e.g., page 4, lines 44-47, which disclose that "PS-O represents an alkoxide residue of any of the free hydroxyl groups of a polysaccharide derivative (PS-OH)." Thus, the Larsen et al. patent teaches non-selective coupling that will result in a mixture of conjugates in which any free hydroxyl group of the polysaccharide is reacted with a suitable functional group of the drug. The Larsen et al. patent contains no teaching whatsoever with regard to linking an aldehyde group of HAS to an active agent, much less any teaching with regard to *specifically linking* the terminal aldehyde group of HAS to an active agent.

With respect to claim 74, Applicants note that similar to the Adamson publication, at no point does the Larsen et al. patent indicate that a terminal aldehyde was necessarily formed, or that a conjugate was necessarily formed through such an aldehyde. Thus, terminal aldehyde groups were not inherently present in the polysaccharides utilized by Larsen et al. Since the Larsen et al. patent fails to disclose either a conjugate or a process for making a conjugate in which a protein is selectively attached to an aldehyde group of HAS, much less the terminal aldehyde group of HAS, this patent does not anticipate the present claims.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 37-45, 47-56 and 74-78 under 35 U.S.C. § 102(b).

Rejections under 35 U.S.C. § 103

Examiner maintained the rejection of claims 37-45, 47-56 and 74-78 under 35 U.S.C. § 103(a), alleging that they are unpatentable over the Adamson publication or the Larsen et al. patent or EP Patent No. 0 019 403 (the Berger et al. patent) in view of the U.S. Patent No. 5,502,043 (the Weidler et al. patent), for reasons of record. The Examiner also asserted that Applicants' previous arguments were not persuasive, because, e.g., there is no indication in the Berger et al. publication that aldehyde groups are not formed on the terminal unit of the HAS, and because the instant specification allegedly does not clearly define the phrase "terminal aldehyde group of the hydroxyalkylstarch molecule."

Applicants respectfully disagree. First, a person of ordinary skill in the art would understand that the phrase "terminal aldehyde group of HAS" refers to an aldehyde at the terminal saccharide unit of the HAS molecule. Second, the present claims are not obvious over the combinations of cited references. For at least the reasons discussed above, the Adamson publication and the Larsen et al. patent do not teach or suggest making conjugates by selectively coupling (i) the terminal aldehyde group of a HAS molecule, or a functional group derived from this aldehyde group by chemical reaction, with (ii) a functional group of a low molecular weight substance. The Berger et al. patent also fails to teach or suggest selectively functionalizing or coupling a low molecular weight substance to the terminal aldehyde group of a HAS molecule. In fact, the Berger et al. patent discloses that HAS can be coupled to other compounds via any of its free hydroxyl functions. *See*, e.g., page 3, line 63 to page 4, line 3, which disclose, *inter alia*, that HAS has a plurality of hydroxyl groups that provide useful sites for bonding active compounds. The methods disclosed by Berger et al. for activating hydroxyl groups yield mixtures of unspecifically modified HAS molecules.

In addition, with respect to claim 74 and the Examiner's assertion that there is no indication in the Berger et al. publication that aldehyde groups are not formed on the terminal unit of the HAS, Applicants note that the examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. MPEP § 2142. The Berger et al. patent

makes no mention of any aldehyde group on the polymers used therein, much less a terminal aldehyde group. Further, MPEP § 2144.03(A) states:

> Official notice unsupported by documentary evidence should only be taken by the examiner where the facts asserted to be well-known, or to be common knowledge in the art are capable of instant and unquestionable demonstration as being well-known. As noted by the court in *In re Ahlert*, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970), the notice of facts beyond the record which may be taken by the examiner must be "capable of such instant and unquestionable demonstration as to defy dispute" (citing *In re Knapp Monarch Co.*, 296 F.2d 230, 132 USPQ 6 (CCPA 1961)).

In the present case, Applicants submit that it has not been instantly and unquestionably demonstrated that aldehyde groups are formed at the terminal aldehyde of the polymer used by Berger et al., and the Examiner has not met the burden of proving a case of *prima facie* obviousness.

The Weidler et al. patent does not remedy the deficiencies of the other three cited references. This is particularly true given that the Weidler et al. patent fails to teach or suggest any conjugate of HAS and another molecule, much less a conjugate formed by selectively coupling the terminal aldehyde group of HAS to a functional group of another molecule. As such, a person of ordinary skill in the art at the time of Applicants' priority date, reading the Weidler et al. patent in combination with either the Adamson publication, the Larsen et al. patent, or the Berger et al. patent, would not have found it obvious to make a specifically coupled HAS conjugate as recited in the present claims. Accordingly, the cited combinations of references do not render the present claims obvious.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 37-45, 47-56 and 74-78 under 35 U.S.C. § 103(a).

CONCLUSION

Applicants submit that claims 67-56 and 74-78 are in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned agent if such would further prosecution.

Please charge $490 for the Petition for Extension of Time fee, $810 for the Request for Continued Examination fee, and any other charges or credits, to deposit account 06-1050.

Respectfully submitted,

Date:/August 11, 2009/

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